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Applicant:	Brenner et al.
Serial No.:	09/654,328
Confirmation No.:	5793
Filed:	September 1, 2000
For:	METHODS AND COMPOSITIONS FOR TREATMENT OF INFLAMMATORY DISEASE USING CADHERIN-11 MODULATING AGENTS
Examiner:	Haddad, Maher M.
Art Unit:	1644

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to MAIL STOP RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the 14 day of July, 2003.

Edward R Gates

MAIL STOP RCE
Commissioner For Patents
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DECLARATION OF DR. MICHAEL B. BRENNER UNDER 37 CFR §1.132

I, Michael B. Brenner, declare as follows:

1. I am a co-inventor of the above-identified patent application. I make this Declaration in support of the Amendment filed in connection with the above-identified patent application, and in response to the Office Action dated April 18, 2003.

2. This Declaration, in part, details the results of experiments carried out under my direct supervision and control. The results relate to an analysis of antibody production in mice administered a cadherin-11-Fc fusion protein.

3. To address the possibility that the cadherin-11-Fc fusion protein was functioning to ameliorate inflammatory arthritis via induction of anti-cadherin-11 antibodies, C57Bl/6 mice

were injected with either cadherin-11-Fc fusion protein (comprising a human IgG1 Fc domain) or control human IgG1 in phosphate buffered saline (intraperitoneal injection, 50 micrograms/mouse). As a positive control, C57Bl/6 mice were injected with human IgG1 in complete Freund's adjuvant (CFA). Sera were obtained prior to injection (pre-immune), and at weeks 2 and 4 after injection. Antibody (humoral) reactivity to injected material was assayed via ELISA using cadherin-11-Fc fusion protein (comprising a human IgG1 Fc domain) (Figure 1A) or human IgG1 (Figure 1B) coated plates. As seen in Figure 1A, no anti-cadherin-11 antibody activity was detectable in mice 4 weeks after injection of the cadherin-11-Fc fusion protein whereas anti-human IgG is readily detectable in mice injected with human IgG1 in CFA. (n=3 mice/group)

4. There is no evidence of a humoral response following administration of cadherin-11-Fc fusion proteins to mice.

5. The data also demonstrate that systemic administration of the cadherin-11-Fc fusion protein is capable of inducing therapeutic benefit in an arthritis model. The cadherin-11-Fc fusion protein need not be administered locally into the synovium for therapeutic benefit, as suggested by the Examiner.

6. This Declaration is also made, in part, to reiterate the arguments presented in the prior Office Action Response (dated October 28, 2002) relating to the correlation of rheumatoid arthritis (in the data provided) and inflammatory joint disease (in the claims as pending). As stated previously, inflammatory joint disorders, of which rheumatoid arthritis is a species, share several pathological, mechanistic and therapeutic characteristics. Similar symptoms and/or pathologies are observed in inflammatory joint disorders, including signs of inflammation (e.g., erythema, warmth, pain and swelling), systemic symptoms (e.g., prolonged morning stiffness, fatigue, fever, and weight loss), laboratory evidence of inflammation (e.g., elevated erythrocyte sedimentation rate or C-reactive protein level, thrombocytosis, anemia of chronic disease, hypoalbuminemia, the presence of inflammatory effusion with white blood cell counts of greater than 2000/μL). Most importantly, the histopathology which reflects the tissue abnormalities and nature of the tissue injury in these disorders is indistinguishable and is characterized by synovitis

with inflammatory, proliferative and in severe cases, erosive changes. The terms "synovitis" and "inflammatory arthritis" (as opposed to degenerative or osteoarthritis) are commonly used to refer to a group of disorders that affect the same regions of the body (i.e., joints) and involve similar cell types (e.g., including synoviocytes, and immune cells or inflammatory leukocytes). These disorders include but are not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, reactive arthritis, systemic lupus erythrematosus and the arthritides associated with inflammatory bowel disease and infectious disease such as hepatitis. Underlying mechanisms are also thought to be common, and these include immune system involvement. Finally, treatments that are therapeutically effective for rheumatoid arthritis have been shown to be effective in other inflammatory joint disorders. These therapies include treatment with TNF-α neutralizing agents (e.g., infliximab and etanercept) and methotrexate. In view of the art-recognized similarity between inflammatory joint disorders and the ability to treat such diseases with similar agents, treatment of the genus of inflammatory joint disorders as a whole is enabled.

7. I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. And further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the United States code and that such willful false statements may jeopardize the validity of this document and any patent which may issue from the above-identified patent application.

7/12/2003
Date

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Figure 1 A

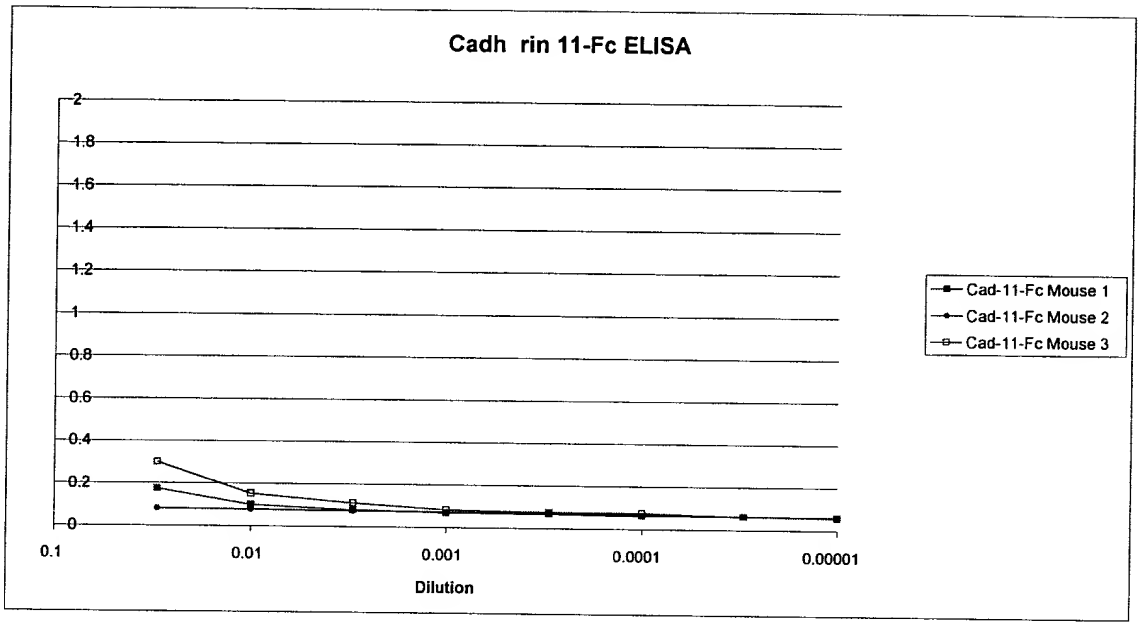

Figure 1B